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Persistent Disparities in Adult Hematopoietic Cell Transplantation

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Abstract The use of large databases has provided advancements in the understanding of racial, ethnic, and socioeconomic disparities in the field of adult hematopoietic cell transplants (HCT). Disparities exist on individual, institutional, and systemic levels for both allogeneic and autologous HCT. We reviewed the most recent publications that utilized large databases to elucidate disparities in HCT and placed them into historical context of the other major studies in the field. Two emerging themes were identified. These themes are persistent inequalities in both allogeneic HCT and autologous HCT for myeloma and the importance of improving homogeneity of care in HCT. Minimization of inequalities can be achieved only with an understanding of the persistent barriers that exist in the field.

Keywords Hematopoietic cell transplants · Health economics · Autologous HCT · Allogeneic HCT

Introduction

The use of a hematopoietic cell transplant (HCT) for the treatment of hematologic cancers can be effective, offering potential cure in universally fatal acute leukemias and prolonged disease remission in lymphomas and plasma cell myeloma. An allogeneic transplant incorporates various myeloablative or non-myeloablative chemotherapies and relies on a donor source for bone marrow rescue and graft-versus-leukemia effect. The best possible source is determined based on human leukocyte antigen (HLA) matching either from a matched related donor (matched sibling) or from large national registry programs for adult donors or umbilical cord blood. The National Marrow Donor Program database collects, analyzes, and coordinates the best possible match of unrelated hematopoietic cells that can be difficult in rare HLA alleles found in minority populations. Autologous HCT provides a non-curative modality to enable high-dose chemotherapies that would be otherwise toxic to the bone marrow with a rescue of the patient's own mobilized stem cells collected just prior to the transplant.

Regardless of the type of HCT, these treatments are complex, costly, and carry considerably higher morbidity and mortality rates than standard chemotherapies. Due to the resources and expertise needed, often these procedures are only attempted in large regional academic centers. Patient adherence to supportive medications and medical appointments can be difficult as it involves significant time and financial resources and a certain degree of medical literacy. While ethnic and racial disparities are present to some degree in all areas of healthcare, concerns about access and outcomes can become magnified by these complex, high-cost, and high-risk therapeutics.

Disparities are defined as differences in the quality of healthcare based on racial or ethnic differences that result in variation in outcomes. While there may be some controversy about the true biological differences between races and ethnic groups, the concept often is used as a surrogate of socioeconomic status, education level, and having health insurance in the USA. Disparities in HCT can provide a window into a

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much more complex and nuanced interpretation about the status of healthcare in the USA and reflect other problems of race in our society. This paper will primarily highlight rates of access to HCT and survival rates following HCT to measure the magnitude of disparities.

Research into HCT disparities has been made possible by harnessing the power of large databases. Most studies utilize their single institution experience or draw data from individual state registries, the Surveillance, Epidemiology, and End Results Program (SEER) database or the Center for International Blood and Marrow Transplant Research (CIBMTR) database. The SEER database, in conjunction with the National Cancer Institute began to track cancer diagnoses in the USA in 1973 and has expanded to include more important epidemiological data for cancer research. The CIBMTR is a research affiliate established in 2004 utilizing the National Marrow Donor Program (NMDP) and International Bone Marrow Transplant Registry (IBMTR) and follows transplant recipient variables and outcomes from over 500 transplant centers worldwide.

Our review paper is meant to highlight the most interesting and important findings in adult HCT disparity research providing a historical background as well as bringing the reader up to date with new studies published in the last year. Several themes have emerged including persistently troubling differences in multiple myeloma care strategies such as lack of access to autologous transplant based on race and socioeconomic status as well as a lagging improvement in overall survival in minority groups with the advancement of new costly medications. Disparities continue to persist for allogeneic transplant access and outcomes. There has been a trend to recognize the importance of homogenizing care patterns to reduce disparities in allogeneic HCT outcomes.

Allogeneic HCT Disparities

Disparities in hematopoietic cell transplantation have been well studied. Much of the literature is in consensus that disparities based on race, ethnicity, and socioeconomic status are prevalent. These disparities exist for survival outcomes following transplant as well as for candidacy to receive a bone marrow transplant. Although available studies focusing on transplant access are somewhat limited, a good example comes from Mitchell and colleagues early on in 1997 who compared both autologous and allogeneic HCT treatments received based on eligible diagnosis from hospital records in several Northeastern states and California between 1988 and 1991. Their group found variation in transplant treatment for either leukemia or lymphoma based on race (Blacks versus Whites) and insurance status [1]. This candidacy hurdle will be echoed by more contemporary studies looking at autologous transplants for myeloma reviewed later in this manuscript.

One of the first major studies to identify race or ethnicity disparities in outcomes for allogeneic HCT was published in 2003 by Serna and colleagues. Their study looked at matched related donor HCT for acute or chronic leukemia in the USA and Canada between 1985 and 1999 utilizing the IBMTR database (now CIBMTR). Compared to Whites, Hispanics had lower 1-year and 3-year adjusted survival rates; however, no other significant differences in survival were found for Blacks or Asians when compared to Whites [2]. Socioeconomic variables such as education, income, and insurance status were not accounted for, and the population consisted of only those that received the transplant. It was not designed to examine the access barriers to transplant or how access barriers contribute to disparities in overall survival for everyone with the diagnosis.

Two years later, this same group led by Baker attempted to identify a particular phase or complication of treatment to explain the somewhat unexpected findings singling out Hispanics' poor survival compared to Whites. The CIBMTR database was utilized again to provide data on matched related donors after myeloablative conditioning for allogeneic HCT in the USA. The study failed to identify differences in the incidence of acute or chronic graft versus host disease, as well as treatment-related mortality, or relapse rates according to racial of ethnic groups. The only significant finding was higher treatment failure and subsequent higher overall mortality for Hispanics. A single transplant-related complication could not be found [3]. Ultimately, they concluded that some ethnically associated biologic variable or sociocultural factor not measured may explain the disparities noted.

Another paper in 2005 found that Hispanics were not the only ethnic group to have worse outcomes following allogeneic HCT. Mielcarek and colleagues reported that their large single-institution database at the Fred Hutchinson Cancer Research Center showed that Blacks had a greater mortality (hazard rate (HR) 1.65; 95 % confidence interval (CI) 1.21–2.25) than Whites after receiving an allogeneic HCT. Biologic variables controlled for included related or unrelated donor, comorbidities, age, donor/patient sex, and CMV exposure. Blacks suffered more acute graft versus host disease and non-relapse mortality. These researches attempted a matched cohort analysis based not only on race but also on other socioeconomic factors which did not seem to alter the mortality hazard ratio to any significant extent [4].

Evidence for socioeconomic differences and allogeneic HCT outcomes had remained elusive until Baker and colleagues returned with their study published in 2009. Patients with either acute or chronic leukemia or myelodysplastic syndrome recorded in the CIBMTR who received unrelated donor myeloablative transplant between 1995 and 2004 were included. Socioeconomic status was estimated from residents' zip codes at the time of transplant. African Americans (AA) had a worse overall survival compared to Whites (HR 1.47,

$p<0.001$) but not Asian or Pacific Islanders or Hispanics. Treatment-related mortality was higher in both AA (HR 1.56, $p<0.001$) and Hispanics (HR 1.30, $p=0.001$). Importantly, all racial groups in the lowest quartile of incomes had worse overall survival and higher risk of treatment-related mortality (HR 1.15 ($p=0.005$) and 1.21 ($p=0.002$), respectively) [5]. This finding of lower-income transcending biologic variables has shifted the focus to systemic-wide problems of class inequality and framed future study designs in this field.

Recent and Important Allogeneic HCT Findings

A single-institution retrospective study from the Mayo clinic in Arizona was published by Khera and colleagues (see Table 1 for a summary of all new studies). They looked at disparities in outcomes following allogeneic hematopoietic stem cell transplantation (HSCT). Of the 296 patients that received an allogeneic transplant from 2003 to 2012, there were 73 % non-Hispanic whites (NHW) and 27 % who self-identified as a minority (largest proportion Hispanic). The two groups showed good parity apart from a younger minority group (median age 40 vs. 54 years) with a lower socioeconomic status. Multivariate analysis showed only higher disease risk, a lower performance status or being a Medicare or Tricare beneficiary versus private insurance holder to be associated with poorer overall survival and progression-free survival. Of particular note is that the category of race/ethnicity did not result in worse survival [6••].

This study suggests a hypothesis that a single institution employing a standardized approach to delivering allogeneic HCT care can reduce or eliminate racial disparities in survival. This hypothesis is intriguing and argues for a more standardized approach and less inter-institutional or provider variability. Important to note, however, this absence of single institutional racial disparity contradicts a previous much larger study by Mielcarek et al. published in 2005. That being said, this much larger retrospective study used a less-contemporary study population with Blacks only accounting for 2 % of the study population [4].

In 2014, a group from Stanford, led by Patel, published an abstract of a retrospective single-institution analysis of their data from 1998 to 2012 very similar to the Mielcarek 2005 study design. They examined mortality and morbidity disparities for both autologous and allogeneic transplants based on race/ethnicity amassing a population size of 3407 to analyze. They found no racial/ethnic disparities in mortality for allogeneic transplant in multivariate analysis among Hispanic, Asian Pacific Islanders, and non-Hispanic Blacks compared to non-Hispanic Whites, but they did find higher odds of GVHD among Asian Pacific Islanders compared with non-Hispanic White recipients (odds ratio (OR) 1.57; 95 % CI (1.06–2.31)) [7].

On the issue of accessing large academic centers, a more recent domestic survey of mostly non-academic medical oncology physician conducted by Pidala et al. found several factors contributing to a lack of HSCT referral. They were a hypothetical patient's age of 60 versus 30 (OR 8.3; 95 % CI 5.9–11.7), having no insurance coverage (OR 6.9; 95 % CI 5.2–9.1), and being African-American versus Caucasian (OR 2.4; 95 % CI 1.9–2.9; $p<0.0001$ all comparisons). The survey further elucidated that the biggest perceived barrier of not referring an African-American for transplant was the lack of availability of unrelated donors. This is despite a 2014 analysis of the NMDP showing that most patients will have an available donor if cord blood is also taken into consideration [8]. The majority of oncologists being surveyed were aware that not all patients had equal access to HSCT consultation with the most common qualitative explanation being related to a lack of insurance [9••].

A recent paper by Patel and colleagues in 2015 emphasizes that Black and Hispanic patients are not able to receive the same treatment as Whites for acute myeloid leukemia (AML) which likely drives disparate outcomes. They looked at California Cancer Registry data linked to hospital discharge abstracts for AML patients between 1998 and 2008. Blacks had decreased odds of receiving chemotherapy (OR 0.74; 95 % CI 0.61–0.91), and both Blacks and Hispanics had decreased odds of transplant (OR 0.64; 95 % CI 0.46–0.87), (OR 0.74; 95 % CI 0.62–0.89), respectively, compared to Whites [10]. Not surprisingly, these Black patients whom did not receive the same treatment had higher mortality (HR 1.14; 95 % CI 1.04–1.25).

Autologous HCT for Myeloma Disparities

Receiving an autologous transplant for a potent but non-curable treatment strategy is still considered the standard of care in the USA for certain hematologic malignancies. The choice to pursue this complex and costly treatment strategy can be influenced by a number of patient considerations. Historically, racial disparities in receiving an autologous transplant were best displayed in a 2010 study published by Joshua and colleagues. Using SEER and CIBMTR data between 1997 and 2002, they showed that Whites were nearly twice as likely (OR 1.72; 95 % CI 1.62–1.83) to receive an autologous HCT compared to Blacks [11]. This is especially troubling considering that the incidence of myeloma is more common among Blacks, especially if the outcomes of transplant are of similar benefit for each race.

To address the question of outcomes, in the same year as the Joshua and colleagues' study on access to autologous HCT was published, a group led by Hari specifically examined racial (Blacks versus Whites) differences in survival of autologous HCT for myeloma. They used the CIBMTR between

Table 1 Summary of recent publications examining disparities in HCT

Reference	Data source	Population size	Characteristics	Results	Conclusion
Costa et al. 2014 [13••]	SEER-18, CIBMTR; 2005–2009	22,462 myeloma and 13,311 transplants	Myeloma cases, NHW 72 %, NHB 18.7 %, Hispanic 6.7 %, Asian 2.6 %	Age-adjusted relative use higher for NHW 1.17 than NHB 0.69, Hispanics 0.64, and Asian 0.65 ($p<0.05$ for all)	Race/ethnicity disparity affects autologous HCT utilization
Pulte et al. 2014 [14••]	SEER; 1998–2009	26,954 divided into 1998–2001, 2002–2005, 2006–2009	Myeloma cases, NHW 63 %, AA 18 %, Hispanic 10 %, API 7 %, aNW 36 %	Mortality HR were 1.2 for AA, 1.25 for Hispanic compared to NHW 2006–2009 ($p<0.05$ for all)	Overall age-adjusted survival increased over time; however, minorities' improvement was less pronounced
Fiala et al. 2015 [15••]	Single institution, SEER; 2000–2009	562, 46,361 divided into tertiles of SES from census ACS and county of home address	Myeloma cases, AA 26 %, 55 % male at institution, 18 % AA, 55 % male in SEER	High, middle, low tertiles OS 62.8, 53.7, 48.6 months ($p=0.015$). Multivariate showed 54 % increased mortality low vs. high SES	Blacks were more likely to be in the low SES which resulted in higher mortality than high SES group locally and in national database
Khera et al. 2014 [6••]	Single Institution; 2003–2012	296 records	Allogeneic HCT, NHW 73 %, 27 % non-White	OS and PFS comparable between groups. High-risk disease, poor PS, Medicare/Tricare predicted mortality	Homogeneity in care at a single institute can overcome racial disparities
Pidala et al. 2013 [9••]	National survey of practicing cancer specialists, non-transplanters	113 survey respondents	Respondents were 68 % male, 62 % NHW, 79 % worked in non-academic setting	Factors affecting no transplant: age OR 8.3, insurance 6.9, race 2.4 ($p<0.05$ for all)	Provider's bias may affect whether a patient is referred for HCT
Patel et al. 2015 [10]	California Cancer Registry; 1998–2008	11,084 records	AML cases, NHW 67 %, AA 5 %, Hispanic 17 %, API 11 %	AA's chemo OR 0.74, AA's and Hispanics' transplants OR 0.64, 0.74. AA's mortality HR 1.14 ($p<0.05$ for all). AA's with treatment HR 1.09 (p=NS)	AA's received less treatment for AML. When AA's received treatment, no morality difference was found

HCT hematopoietic cell transplantation, *SEER* Surveillance Epidemiology and End Results, *CIBMTR* Center for International Blood and Marrow Transplant Research, *NHW* non-Hispanic White, *NHB* non-Hispanic Black, *AA* African American, *API* Asian Pacific Islander, *HR* hazard ratio, *OR* odds ratio, *OS* overall survival, *PFS* progression-free survival, *PS* performance status, *NS* non-significant, *SES* socioeconomic status

1995 and 2005 to find 2195 recipients of autologous transplant for multiple myeloma. Blacks were more likely to be female, younger, and have better performance status yet were more likely to be transplanted later in their treatment course. Importantly, no differences between race was seen in a 5-year overall survival, progression, or non-relapse mortality [12]. This confirmed a previous finding of no difference in survival outcomes between Blacks and Whites in this treatment setting [4].

Recent and Important Myeloma Care Disparities

Several papers highlighting racial inequalities were published in the last year regarding myeloma care. Costa and colleagues retrospectively examined the SEER and the CIBMTR database during the years of 2005-2009 for relative utilization of an autologous transplant for different groups in an entire population. Over 22,000 myeloma cases with over 13,000 autologous transplants were conducted during the period of study. Disparities existed in age-adjusted relative utilization rates (RURs) of autologous HCT for multiple myeloma for non-Hispanic Whites (NHW) 1.17 (95 % CI 1.15–1.19), non-Hispanic Blacks (NHB) 0.69 ($p<0.0002$), Hispanics 0.64 ($p<0.002$), and Asians 0.65 ($p<0.0002$) (figures lower than 1.0 represent lower utilization). The SEER database began tracking data on insurance status in 2007. These researchers found that only 3.1 % of NHW under age 65 were uninsured compared to 8.1 % NHB, 11.9 % Hispanics, and 13.5 % Asians ($p<0.001$) [13••]. Race/ethnicity has been postulated as the primary hurdle to receive an autologous transplant.

Interestingly, sex disparities were most evident for Hispanics with 10.4 % of women not receiving autologous transplants [13••]. Some of the sex discrepancies seen in the non-Hispanic groups disappeared when adjusting for age suggesting that women's later age at diagnosis prevented the transplant. These findings on race and gender echo a prior study mentioned above reporting Whites more likely than Blacks (OR 1.72; 95 % CI 1.62–1.83) and males more than females (OR 1.1; 95 % CI 1.07–1.13) to received an autologous HCT [11]. Given that autologous transplants were certainly regarded as the standard of care during these years, these age-adjusted numbers provided by Costa show a deep division in the evolving field of myeloma care that is persistent and worrisome.

Also published in the last year was a study by Pulte and colleagues that found a relative improvement in myeloma survival according to different racial and ethnic groups between the time periods of 1998–2001 and 2006–2009. Using the SEER database, survival- and disease-related mortalities were compared accounting for the complete package of myeloma care, not just autologous transplant utilization. While the relative overall 5-year survival increased from 35.6 to 44 % ($p<0.0001$) during these time periods, young (<50) non-Hispanic Whites enjoyed a 16.8 % ($p<0.0001$) improvement and young AA also improved by 14.4 % ($p=0.01$). However, there was not a statistically significant improvement between these two time periods for either Hispanics or Asian and Pacific Islanders. Additionally, excess mortality hazard ratios from 2006 to 2009 were 1.2 (95 % CI 1.09–1.33) for AA and 1.25 (95 % CI 1.11–1.41) for Hispanics compared to NHW [14••]. Like many areas of rapidly evolving oncology care, newer treatments are more expensive leaving ethnic minorities, who are often at a lower socioeconomic status, failing to benefit at a similar rate.

A third important study came from Fiala and colleagues who attempted to further tease out the difference between race and ethnicity from socioeconomic status. They looked at 652 myeloma patients from Washington University in St. Louis from 2000 to 2009 and validated their single-institution findings by running a similar analysis on the SEER database during those years. This epidemiological approach controlled for race, age, year of diagnosis, severity of comorbidities, transplant utilization, and insurance provider. Socioeconomic status (SES) was approximated from the median household income obtained from the census tract of the American Community Survey and was divided into three groups. Comparing low, median, and high SES groups, median overall survival was 48.6, 53.7, and 62.8 months, respectively ($p=0.015$). The SEER database analysis found a mortality risk of 1.18 (95 % CI 1.15–1.22) for low and 1.10 (95 % CI 1.07–1.13) for medium SES when compared to high SES [15••]. Clearly, myeloma care is a complex issue, but expense of treatment and the impact on doctors and patients' choices are promoting a tiered outcome discrepancy.

It should be mentioned that with the advent of many new drugs and their combinations for myeloma treatment, there is current controversy about how autologous transplant should be used or even if it should be used at all. Essentially, because this type of transplant is not curative and carries with it significant cost and potential morbidity, there is a camp of providers that believe the improved effectiveness of newer drug combinations may provide equal long-term benefit as early transplant modalities. Finding the superior approach will take some time using rigorous prospective studies. Regardless of the choice of transplant, a bigger crisis of affordability of these new treatment options will continue to maintain and potentially widen disparities in race, ethnicity, and SES.

Discussion

While recent studies examining both allogeneic transplant approaches to adult acute leukemia and autologous approaches to myeloma emphasize persistent disparities in outcomes, there were several papers hitting on the theme of standardization of allogeneic HCT cares. The concept of homogeneity of

transplant health care was recently reviewed by Loberiza and colleagues pointing out the lack of consensus and standardization of practice among institutions and even among providers in the same treatment center [16]. An international survey by Lee et al. highlighted that agreement on management of graft versus host disease and even intensity of conditioning regimen varied among physicians [17]. Perhaps this is due to a lack of consistent guidelines as a 2011 review of US and European guidelines found considerable variation between them and those given by the literature [18]. It is unclear what methods can be employed to improve homogeneity in care, but use of peer practice pattern comparisons or standardized care models with electronic decision support has been suggested to improve adherence to what can be agreed to be a standard of care.

Adhering to evidence-based standards of care may have been successful in elimination of Black and White survival disparities outside of transplant care. This has been demonstrated in a notable paper by Onega et al. in 2010. They looked at all-cause and cancer-specific mortality for Medicare patients receiving care for the four most common types of cancer in the USA at National Cancer Institute-designated comprehensive or clinical cancer centers. The higher 1- and 3-year mortalities seen in breast, lung, colon, and prostate cancers for AA were eliminated when care was received at NCI-designated centers, many of which are academic centers [19]. This suggests that institutions with better infrastructure to deliver appropriate evidence-based, timely, and more standardized care may reduce disparate survival outcomes for common cancers.

Access to large institutions depends on geographical barriers but also monetary barriers with having appropriate insurance. Given that Khera and colleagues found a difference in survival based on type of patient's insurance [6••], this also brings up an interesting debate of the importance of private versus federal programs that is timely given the changing healthcare landscape in the USA with the Affordable Care Act. With increasing options in insurance plans found on insurance marketplaces since the implementation of the Affordable Care Act (ACA), future scrutiny will have to judge adequate or appropriate plans on the marketplace. Medicare's coverage has shaped private insurer's coverage for many years in the USA, and there is no reason for discrepancy of coverage to exist between private and federal plans. While some aspects of federally mandated coverage are polemic, assuring coverage of life-saving therapies surely is not.

It may no longer be enough simply to have health insurance as mandated by the ACA but actually to have insurance plans that do not impede access to expensive and complex procedures like an HCT. Attempts to increase the quantity of health care coverage in the USA with efforts like the ACA and Medicaid expansion should not be deemed successful without first paying careful attention to the quality of that care expansion. For example, there can be substantial variation in Medicaid coverage for HCT by state [20]. Many plans leave patients feeling underinsured when faced with their portion of the bill and considering the time missed from employment. It is no wonder that many transplant survivors experience significant financial hardships despite having insurance coverage [21].

There are, of course, limitations harnessing large databases for disparities research. Concluding cause and effect of mortality or morbidity based on retrospective data is impossible, just as randomizing groups based on race/ethnicity or socioeconomic status for prospective analysis is impossible due to ethical reasons. At best, we are left with imperfect groupings of populations who may be more heterogeneous than implied by a group of similar socioeconomic identical race individuals from which to draw conclusions. Socioeconomic status is particularly difficult due to lack of individual SES data, changing SES over a lifetime, and using surrogate markers such as zip codes for estimation. Race and ethnicity is problematic due to the dual genetic and social aspects of race, increasingly genetically diverse individuals, and variations in any one individual's health care access and literacy within a racial group. Despite these limitations, health disparities cannot be ignored, just interpreted with a nuanced understanding.

Conclusion

Disparities based on race, ethnicity, and socioeconomic status are pervasive in allogeneic and autologous HCT access and outcomes. Problems can exist at the individual, institutional, or systemic level and are magnified when considering the expensive and complex aspects of treatment. Harnessing the power of large databases such as SEER and CIBMTR has advanced the understanding and awareness of these disparities. Although the use of these databases is not without limitations, they facilitate the generation of hypotheses that allows further examination. As demonstrated in the last year, several studies have stood out in their advancement of the field drawing attention to the disparities in myeloma care regardless of autologous transplant and the importance of standardizing care patterns in allogeneic transplant. A simultaneous approach of changing individual doctors and patient's biases, institutional practices, and systemic health insurance coverage is needed to eliminate disparities in HCT care.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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